UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/226,895	01/07/1999	MICHAEL ROSENBLUM	D6205	8983

27851 7590 08/12/2002

BENJAMIN A. ADLER
8011 CANDLE LANE
HOUSTON, TX 77071

EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/12/2002 15

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 15

Application Number: 09/226,895
Filing Date: January 7, 1999
Appellant(s): Rosenblum et al

Benjamin Aaron Adler
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed January 9, 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's state that all the pending claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

There is no new prior art of record.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 7-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta et al (Proceedings of the American Association for Cancer Research, 1997, Vol. 38, p. 88) in view of Flavell et al (Cancer Research, 1997, Vol. 57, pp. 4824-4829).

Claims 1, 5-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta et al, 1997 and Flavell et al as applied to claims 1, 7-9 and 11 above, and further in view of Mehta et al (Proceeding of the American society for Cancer Research, 1994, Vol. 35, p. 92).

Mehta et al (1997) teach that the use of immunotoxins for killing tumor cells is limited by heterogenous expression of the target antigen on said tumor cell (abstract, lines 1-4). Mehta et al teach that this problem can be overcome by the administration of an agent which can induce high levels of the target antigen on tumor cells thereby increasing the effectiveness of the immunotoxin. Mehta et al specifically teach that retinoic acid increases the expression of the target antigen, CD38, on leukemia cells and cell lines. Mehta et al demonstrate that the retinoic acid treatment of a leukemia cell line increases the toxicity of anti-CD38-gelonin by a factor of 10^4 to 10^6 in comparison with cells treated only with anti-CD38-gelonin. Mehta et al do not demonstrate the in vivo treatment of patients by said combination method.

Flavell et al teach that the use of immunotoxins for killing tumor cells is limited by heterogenous expression of the target antigen on said tumor cells (Introduction, first paragraph). Flavell et al teach that this problem can be overcome by the targeting of three separate antigens present on the tumor cells. Flavell et al specifically teach the killing of a human B-cell lymphoma growing in immuno deficient mice by means of administration of anti-CD38 immunotoxin in addition to anti-CD19 and anti-CD22 immunotoxin. Flavell et al teach that the anti-CD38 immunotoxin had some effectiveness against the B-cell lymphoma in vivo (page 4826, second column, under "Survival" lines 11-13) but was more effective when combined with anti-CD19 and anti-CD22 immunotoxin due to the lack of adequate CD38 expression on all the tumor cells.

(11) Response to Argument

Appellants argue that there is no suggestion to combine the teachings of Flavell et al and Mehta (1997) et al (page 6, last line to page 7, line 2). The examiner disagrees with this assertion and believes that Mehta et al (1997) teaches the motivation to combine with Flavell et al, and conversely, Flavell et al teaches the motivation to combine with Mehta et al.

A problem in the treatment of tumors by antibodies conjugated to toxins is in achieving adequate delivery of the antibody-toxin conjugate to all cells in a tumor population so that all tumor cells will be destroyed. In a given population of tumor cells, not all the cells will express a cell surface target antigen to the same extent. Thus for the sub-population of tumor cells expressing the target antigen at a lower density, the delivery of a toxin via an antibody-conjugate targeted to the antigen will not result in an adequate dose of toxin to the cells of that particular subpopulation. This subpopulation of tumor cells will exhibit resistance to the antibody-toxin. Mehta et al (1997) state that "The use of monoclonal antibodies for delivering toxins to cell surface molecules expressed by tumor cells is limited due to heterogenous expression of the target antigen". Corroborating these teachings, Flavell et al state "Heterogeneity of target antigen expression is a major limiting factor that determines the success of any antibody based therapy for cancer in which delivery of a cytotoxic agent to all malignant cells with growth potential within the tumor is essential for total tumor ablation". Mehta et al (1997) teach that a solution to this problem is to upregulate the expression of the target antigen, "Agents capable of inducing high levels of cell surface target molecules on tumor cells could circumvent this problem". An increase in cell surface target antigen throughout the entire tumor cell population would lead to an increase in cell surface antigen in the subpopulation of cells that was formerly resistant to therapy with the antibody-toxin conjugate. The IB4 monoclonal antibody specifically binds the CD38 antigen that is expressed on the surface of leukemia cells. Mehta et al (1997) disclose that retinoic acid was capable of increasing the level of cell surface CD38 antigen in several leukemia cell lines. Mehta et al (1994) demonstrated increased cytotoxicity to IB4-gelonin when leukemia cells in culture were

pretreated with retinoic acid. Mehta et al point out that normal granulocytes which did not normally produce the CD38 antigen, did not produce CD38 cell surface antigen after treatment with the retinoic acid and as a consequence were resistant to IB4-gelonin cytotoxicity. Mehta et al concludes "The potent effect of retinoids on cell surface expression of CD38 antigen coupled with the specific cytotoxicity of the IB4/rGEL [recombinant gelonin] suggests that this approach may have clinical utility in terms of treating certain leukemias". One of skill in the art would conclude from these teachings of Mehta et al(1997) that the combination therapy of IB4-gelonin and retinoic acid would be appropriate in cases where the leukemic cells were expressing CD38 cell surface antigen, and further that normal cells not expressing the CD38 antigen will not be targeted by this treatment. Mehta et al (1994) have previously demonstrated that a significant increase in CD38 cell surface antigen expression was observed in vivo after administering ATRA (all trans retinoic acid) to patients with myeloid leukemia.

Flavell et al corroborate the teachings of Mehta et al (1997) on the challenge of overcoming antigen heterogeneity in therapies based on antibody-toxin conjugates (page 4824, first line). Flavell et al teach the anti CD38-saporin conjugate of the instant invention. One can see from Table 4 (page 4826) that the survival time of mice carrying human lymphoma cells was more than doubled by the administration of the anti CD-38 saporin conjugate alone (line 2 versus line 26 of Table 4). Flavell et al do not teach the upregulation of CD38 antigen on the tumor cell population as a means for increasing antigen cell surface density in the subpopulation of tumor cells expressing the target antigen at lower density. Flavell et al teach the targeting of multiple cell surface antigens on tumor cells as a means of overcoming resistance to antibody-immunotoxin conjugates. Flavell et al reason that although it would be possible for any given tumor cell to underexpress a particular cell surface antigen, it would be statistically unlikely for that tumor cells to underexpress three different cell surface antigens (page 4824, second paragraph under the "introduction" and Table 1 on page 4825). Thus Flavell et al combined the anti CD38-saporin conjugate, OKT10-saporin (page 4825, table 2),

with an anti-CD19 saporin conjugate and an anti-CD22 saporin conjugate for the maximum therapeutic efficacy measured in mean survival days (Table 4, line 7).

Thus one of skill in the art would be motivated to combine the teachings of Flavell et al and Mehta et al. Flavell teaches that the anti-CD38 saporin conjugate is cytotoxic to human lymphoma cells in vivo. Mehta et al (1994) teach that the administration of ATRA [all trans retinoic acid) upregulates CD38 target antigen on the surface of myelocytic leukemia cells when administered in vivo. Mehta et al (1997) teach that retinoic acid increases the susceptibility of leukemia cells to the cytotoxic action of an anti CD38-gelonin conjugate. Given the teachings of all three references it would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the anti-CD38-saporin conjugate taught by Flavell for the anti-CD38-gelonin conjugate as taught by Mehta (1997) in a combination with retinoic acid. It would then have been further obvious that this combination could be applied to the treatment of tumors in vivo, as Flavell has taught that anti-CD38 conjugated to saporin has efficacy against human tumor cells in vivo and Mehta et al (1994) has taught the upregulation of CD38 antigen on myeloid leukemia cells in vivo by administration or an oral dose of ATRA. One of skill in the art would have expected that for patients suffering from myeloid leukemias or lymphomas, administration of retinoic acid would upregulate the CD38 antigen on the tumor cells, making the total population of tumor cells more susceptible to binding of the CD38 saporin conjugate, and resulting in increased toxicity to the total tumor cell population and increased survival times of the patients.

Appellants argue that Mehta et al did not provide additional teachings to suggest the combination of retinoic acid and a single anti-CD38 immunotoxin would be an effective treatment against leukemia or lymphoma (page 6, lines 18-21). Appellants further argue that without actually attempting the combination in a manner analogous to that of the instant invention, a person having ordinary skill in the art would not be able to determine that retinoid stimulation of CD38 would enable Flavell's immunotoxin to be used as the sole administered immunotoxin, without undue experimentation (page 8, lines 6-14). It is noted that the instant

specification provides objective evidence that the killing of cell lines in vitro is augmented by retinoic acid, but does not provide an example of an in vivo treatment of leukemia or lymphoma. The instant specification does not set forth an example wherein the administration of retinoids and anti-CD38 immunotoxin kills tumor cells in a patient. Mehta et al (1997) provides objective evidence that the killing of cell lines in vitro is augmented by retinoic acid and suggest the utility of the combination method for clinical treatment (last line of abstract). Thus the teachings of the instant specification are commensurate with the teachings of Mehta et al, specifically, that evidence of cell killing in vitro is a nexus for cell killing in vivo, however, the teachings of the instant specification do not surpass the teachings of Mehta et al (1997) with respect to the efficacy of the combination therapy administered to a patient in need thereof.

Appellants argue that the main point of Flavell et al was that the anti-CD38 immunotoxin must be administered with two other immunotoxins to be fully effective, not that the administration of the single immunotoxin directed against anti-CD38 was somewhat effective (page 7, lines 11-16). This is not a persuasive argument as Flavell et al do disclose some effect from the anti-CD38 immunotoxin and the M.P.E.P. (2123) states that preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ423 (CCPA 1971). Thus the preferred embodiment of administration of a triple immunotoxin cocktail does not teach away from the fact that administration of the anti-CD38 immunotoxin as a sole immunotoxin had a limited efficacy.

Appellants argue that one of skill in the art, after a clear reading of Flavell et al, would not resort back to the use of a single immunotoxin with or without retinoid boosted antigenic expression (page 7, line 17 to page 8, line 5). Flavell et al discuss (beginning on page 4828, second column, line 23) the observation that treatment of mice with one or two different immunotoxins resulted in residual tumors comprising cells that persisted in the expression of the target antigens. Flavell et al concludes (page 4829, lines 17-19 and lines 7-10) that a small fraction of tumor cells were down-regulated for antigen expression at the time of treatment

with the immunotoxins thereby escaping death. Upon the clear reading of Flavell et al and a clear reading of Mehta et al (1997) one of skill in the art would indeed conclude that the teachings of Mehta et al on the up-regulation of target CD38 antigen remedy the deficiency of Flavell et al, on the evasion of tumor cell death by the down-regulation of target antigen at the time of treatment. One of skill in the art would be motivated to combine said teachings in order to prevent the evasion of tumor cell death by down regulation of CD38 at the time of treatment.

Appellants argue that between the publications of Mehta et al (1997) and Flavell et al (1997), and the instant application, there were no publications wherein one of skill in the art actually combined the teachings of Mehta et al and Flavell et al, and therefore, the motivation to combine said teachings could not have been obvious to one of skill in the art (page 8, line 19 to page 9, line 3). This is not persuasive as it is well known in the art that an experimental protocol involving the treatment of an individual having a pathophysiological state requires extensive preparation and planning on issues such as how to assess the safety of the proposed treatments, how to monitor the actual progress of the patients, and how to assure data accuracy and protocol compliance. In view of the time necessary to complete the detailed planning and preparations, as well as to complete and compile the experimental evidence after the claimed combination therapy, one of skill in the art would not be able to publish a finished work in less than two years after the publication of Mehta et al and Flavell et al. Therefore, the lack of a publication regarding the proposed combination therapy is not indicative that the combination in non-obvious, only that it requires a lengthy time to plan, treat and assess the results of an in vivo treatment before publication of the results.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Karen A. Canella, Ph.D.
March 26, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
Conferee